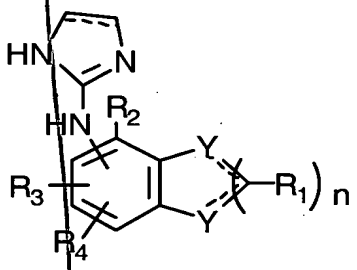
CLAIMS

Having now described the invention, what is claimed is:

1) A topical ophthalmic composition useful for controlling elevated intraocular pressure associated with glaucoma and ocular hypertension while providing neuroprotection to the ocular nerves, comprising a combination of a therapeutically effective amount of a prostaglandin and a therapeutically effective amount of an alpha adrenergic agent of formula (I)



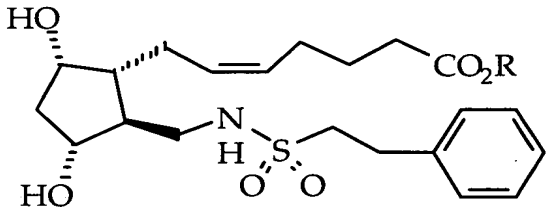
formula (I)

wherein each Y is independently selected from the group consisting of N, N-CH3, O, S and C-R_1; R_1 is hydrogen, lower alkyl or oxo; R_2, R_3 and R_4 are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkenyl; n is an integer from 1 to 3; and a broken line beside a solid line indicates a single or double bond, provided that two double bonds are not on the same carbon in the case when n=1, and their pharmaceutically acceptable salts and esters as appropriate.

2) The composition of claim 1 wherein the prostaglandin is selected from the group consisting of $PGF_{2\alpha}$, PGE_2, PGE_1, prostacyclin, 15(S)-methyl-$PGF_{2\alpha}$, 16,16-dimethyl-$PGF_{2\alpha}$, 15(S)-methyl-PGE_2, 16,16-dimethyl-PGE_2, 17,18,19,20-tetranor-16-phenoxy-PGE2, 17,18, 19,20-tetranor-16-phenoxy-$PGF_{2\alpha}$, 18,19,20-trinor-17-phenyl-PGE_2, 18,19,20-trinor-17-phenyl-$PGF_{2\alpha}$, the free acid and lower alkyl esters of $PGF_{2\alpha}$ wherein the omega chain has been replaced with phenylethylsulfonamidomethyl- , trimoprostil, RS-84-135, rioprostil,

S-1033 (15-deshydroxy $PGF_{2\alpha}$, sodium salt), S-747260, nocloprost, CS-412, YPG-209, K-10134, cloprostenol, fluprostenol, luporstiol, etiproston, tiaprost, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 118182, 13,14-dihydro-ZK 118182, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41 (latanoprost), RO-221327, HR-466, HR-601, ONO-1206, UFO-21, 11-deoxy-PGE_2, 11-deoxy-$PGF_{2\alpha}$, 11-deoxy-16,16-dimethyl-PGE_2, 11-deoxy-15(S)-methyl-PGE_2, 11-deoxy-15(S)-methyl-$PGF_{2\alpha}$, misoprostol, enisoprost, MDL-646, CL-115,574, CL-115,347, TR-4161, TR-4752, TR-4367, CP-27987, sulprostone, gemeprost, alfaprostol, delprostenate, prostalene, fenprostalene, CL-116,069, ONO-995 and RO-229648, and their pharmaceutically acceptable esters and salts, as appropriate.

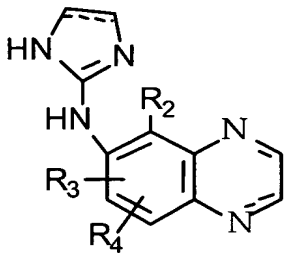
3) The composition of claim 2 wherein the prostaglandin is selected from the group consisting of $PGF_{2\alpha}$-11-pivalyl ester, the 1-amido-15-methyl ether of $PGF_{2\alpha}$, 1-ethylamido-18,19,20-trinor-17-phenyl-$PGF_{2\alpha}$, $PGF_{2\alpha}$-1-ethyl ester, $PGF_{2\alpha}$1-isopropyl ester, the acid and isopropyl ester derivatives of $PGF_{2\alpha}$ wherein the omega chain has been replaced with phenylethylsulfonamidomethyl-, as represented by the structure below:



R=H, i-propyl,

RO-229648, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41, and 18,19,20-trinor-17-phenyl-$PGF_{2\alpha}$-1-methyl ester.

4) The composition of claim 1 wherein the alpha adrenergic agent is further selected from formula (I) to contain the groups of formula (II) wherein R2 is bromine or methyl and all other variables are defined as in claim 1.

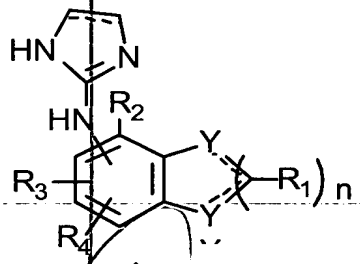


formula (II)

5) The composition of claim 3 wherein the alpha adrenergic agent is brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine).

6) The composition of claim 4 wherein the alpha adrenergic agent is brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine).

7) A method of treating a mammal suffering from glaucoma or ocular hypertension, comprising administering to the mammal a therapeutically effective amount of a prostaglandin and a therapeutically effective amount of an alpha adrenergic agent of formula (I)

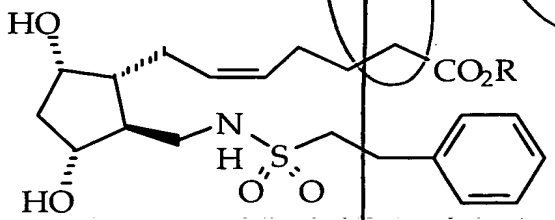


formula (I)

wherein each Y is independently selected from the group consisting of N, N-CH3, O, S and C-R_1; R_1 is hydrogen, lower alkyl or oxo; R_2, R_3 and R_4 are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkenyl; n is an integer from 1 to 3; and a broken line beside a solid line indicates either a single or a double bond, provided that two double bonds are not on the same carbon in the case when n=1, and their pharmaceutically acceptable salts and esters as appropriate.

8) The method of claim 7 wherein the prostaglandin is selected from the group consisting of $PGF_{2\alpha}$, PGE_2, PGE_1, prostacyclin, 15(S)-methyl-$PGF_{2\alpha}$, 16,16-dimethyl-$PGF_{2\alpha}$, 15(S)-methyl-PGE_2, 16,16-dimethyl-PGE_2, 17,18,19,20-tetranor-16-phenoxy-PGE2, 17,18, 19,20-tetranor-16-phenoxy-$PGF_{2\alpha}$, 18,19,20-trinor-17-phenyl-PGE_2, 18,19,20-trinor-17-phenyl-$PGF_{2\alpha}$, the free acid and lower alkyl esters of $PGF_{2\alpha}$ wherein the omega chain has been replaced with phenylethylsulfonamidomethyl- , trimoprostil, RS-84-135, rioprostil, S-1033 (15-deshydroxy $PGF_{2\alpha}$, sodium salt), S-747260, nocloprost, CS-412, YPG-209, K-10134, cloprostenol, fluprostenol, luporstiol, etiproston, tiaprost, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 118182, 13,14-dihydro-ZK 118182, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41 (latanoprost), RO-221327, HR-466, HR-601, ONO-1206, UFO-21, 11-deoxy-PGE_2, 11-deoxy-$PGF_{2\alpha}$, 11-deoxy-16,16-dimethyl-PGE_2, 11-deoxy-15(S)-methyl-PGE_2, 11-deoxy-15(S)-methyl-$PGF_{2\alpha}$, misoprostol, enisoprost, MDL-646, CL-115,574, CL-115,347, TR-4161, TR-4752, TR-4367, CP-27987, sulprostone, gemeprost, alfaprostol, delprostenate, prostalene, fenprostalene, CL-116,069, ONO-995 and RO-229648, and their pharmaceutically acceptable esters and salts, as appropriate.

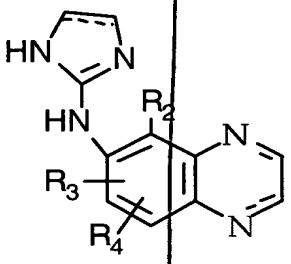
9) The method of claim 8 wherein the prostaglandin is selected from the group consisting of $PGF_{2\alpha}$-11-pivalyl ester, the 1-amido-15-methyl ether of $PGF_{2\alpha}$, 1-ethylamido-18,19,20-trinor-17-phenyl-$PGF_{2\alpha}$, $PGF_{2\alpha}$-1-ethyl ester, $PGF_{2\alpha}$1-isopropyl ester, the acid and isopropyl ester derivatives of $PGF_{2\alpha}$ wherein the omega chain has been replaced with phenylethylsulfonamidomethyl-, as represented by the structure below:



R=H, i-propyl,

RO-229648, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41, and 18,19,20-trinor-17-phenyl-$PGF_{2\alpha}$-1-methyl ester.

10) The method of claim 7 wherein the alpha adrenergic agent is further selected from formula (I) to contain the groups of formula (II) wherein R2 is bromine or methyl and all other variables are defined as in claim 7.



formula (II)

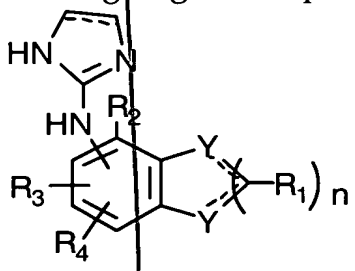
11) The method of claim 9 wherein the alpha adrenergic agent is brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine).

12) The method of claim 10 wherein the alpha adrenergic agent is brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine).

13) The method of claim 7 wherein the prostaglandin is the 11-pivalyl ester of $PGF_{2\alpha}$ and the alpha adrenergic agent is brimonidine.

14) An article of manufacture comprising packaging material and a pharmaceutical combination of at least one alpha adrenergic agent and at least one prostaglandin and their pharmaceutically acceptable salts and esters as appropriate contained within said packaging material, wherein the pharmaceutical agents are effective in controlling elevated intraocular pressure associated with glaucoma and ocular hypertension and wherein the packaging material comprises a label which indicates that said combination can be used

for control of elevated intraocular pressure or in treating glaucoma, and wherein said alpha adrenergic agent is represented by formula (I)



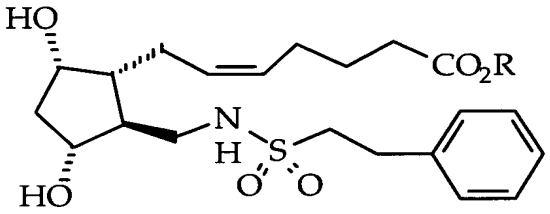
formula (I)

wherein each Y is independently selected from the group consisting of N, N-CH3, O, S and C-R_1; R_1 is hydrogen, lower alkyl or oxo; R_2, R_3 and R_4 are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkenyl; n is an integer from 1 to 3; and a broken line beside a solid line indicates a single or double bond, provided that two double bonds are not on the same carbon in the case when n=1.

15) The article of claim 14 wherein the prostaglandin is selected from the group consisting of $PGF_{2\alpha}$, PGE_2, PGE_1, prostacyclin, 15(S)-methyl-$PGF_{2\alpha}$, 16,16-dimethyl-$PGF_{2\alpha}$, 15(S)-methyl-PGE_2, 16,16-dimethyl-PGE_2, 17,18,19,20-tetranor-16-phenoxy-PGE2, 17,18, 19,20-tetranor-16-phenoxy-$PGF_{2\alpha}$, 18,19,20-trinor-17-phenyl-PGE_2, 18,19,20-trinor-17-phenyl-$PGF_{2\alpha}$, the free acid and lower alkyl esters of $PGF_{2\alpha}$ wherein the omega chain has been replaced with phenylethylsulfonamidomethyl- , trimoprostil, RS-84-135, rioprostil, S-1033 (15-deshydroxy $PGF_{2\alpha}$, sodium salt), S-747260, nocloprost, CS-412, YPG-209, K-10134, cloprostenol, fluprostenol, luporstiol, etiproston, tiaprost, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 118182, 13,14-dihydro-ZK 118182, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41 (latanoprost), RO-221327, HR-466, HR-601, ONO-1206, UFO-21, 11-deoxy-PGE_2, 11-deoxy-$PGF_{2\alpha}$, 11-deoxy-16,16-dimethyl-PGE_2, 11-deoxy-15(S)-methyl-PGE_2, 11-deoxy-15(S)-methyl-$PGF_{2\alpha}$, misoprostol, enisoprost, MDL-646, CL-115,574, CL-115,347, TR-4161, TR-4752, TR-4367, CP-27987, sulprostone, gemeprost, alfaprostol, delprostenate, prostalene, fenprostalene, CL-116,069,

ONO-995 and RO-229648, and their pharmaceutically acceptable esters and salts, as appropriate.

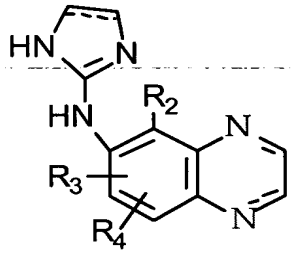
16) The article of claim 15 wherein the prostaglandin is selected from the group consisting of $PGF_{2\alpha}$-11-pivalyl ester, the 1-amido-15-methyl ether of $PGF_{2\alpha}$, 1-ethylamido-18,19,20-trinor-17-phenyl-$PGF_{2\alpha}$, $PGF_{2\alpha}$-1-ethyl ester, $PGF_{2\alpha}$1-isopropyl ester, the acid and isopropyl ester derivatives of $PGF_{2\alpha}$ wherein the omega chain has been replaced with phenylethylsulfonamidomethyl-, as represented by the structure below:



R=H, i-propyl,

RO-229648, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41, and 18,19,20-trinor-17-phenyl-$PGF_{2\alpha}$-1-methyl ester.

17) The article of claim 14 wherein the alpha adrenergic agent is further selected from formula (I) to contain the groups of formula (II) wherein R2 is bromine or methyl and all other variables are defined as in claim 14.



formula (II)

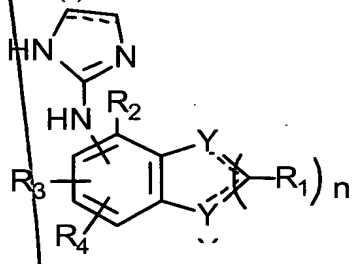
18) The article of claim 16 wherein the alpha adrenergic agent is brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine).

19) The article of claim 17 wherein the alpha adrenergic agent is brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine).

20) The article of claim 14 wherein the prostaglandin is the 11-pivalyl ester of $PGF_{2\alpha}$ and the alpha adrenergic agent is brimonidine.

Sub A3

21) A method of preventing degeneration of the optic nerve and providing protection of the retinal ganglion cells of a mammal suffering from glaucoma or ocular hypertension, comprising administering to the mammal a therapeutically effective amount of a prostaglandin and a therapeutically effective amount of an alpha adrenergic agent of formula (I)



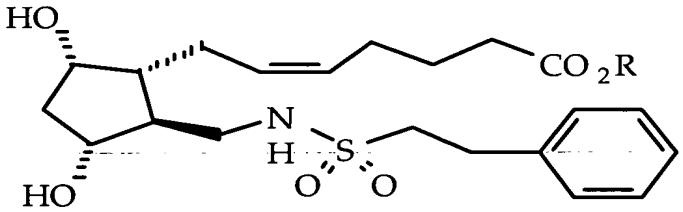
formula (I)

wherein each Y is independently selected from the group consisting of N, N-CH3, O, S and C-R_1; R_1 is hydrogen, lower alkyl or oxo; R_2, R_3 and R_4 are independently selected from the group consisting of hydrogen, halogen, lower alkyl and lower alkenyl; n is an integer from 1 to 3; and a broken line beside a solid line indicates either a single or a double bond, provided that two double bonds are not on the same carbon in the case when n=1, and their pharmaceutically acceptable salts and esters as appropriate.

22) The method of claim 21 wherein the prostaglandin is selected from the group consisting of $PGF_{2\alpha}$, PGE_2, PGE_1, prostacyclin, 15(S)-methyl-$PGF_{2\alpha}$, 16,16-dimethyl-$PGF_{2\alpha}$, 15(S)-methyl-PGE_2, 16,16-dimethyl-PGE_2, 17,18,19,20-tetranor-16-phenoxy-PGE2, 17,18, 19,20-tetranor-16-phenoxy-$PGF_{2\alpha}$, 18,19,20-trinor-17-phenyl-PGE_2, 18,19,20-trinor-17-phenyl-$PGF_{2\alpha}$, the free acid and lower alkyl esters of

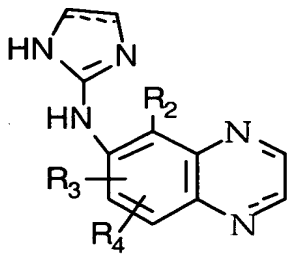
$PGF_{2\alpha}$ wherein the omega chain has been replaced with phenylethylsulfonamidomethyl- , trimoprostil, RS-84-135, rioprostil, S-1033 (15-deshydroxy $PGF_{2\alpha}$, sodium salt), S-747260, nocloprost, CS-412, YPG-209, K-10134, cloprostenol, fluprostenol, luporstiol, etiproston, tiaprost, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 118182, 13,14-dihydro-ZK 118182, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41 (latanoprost), RO-221327, HR-466, HR-601, ONO-1206, UFO-21, 11-deoxy-PGE_2, 11-deoxy-$PGF_{2\alpha}$, 11-deoxy-16,16-dimethyl-PGE_2, 11-deoxy-15(S)-methyl-PGE_2, 11-deoxy-15(S)-methyl-$PGF_{2\alpha}$, misoprostol, enisoprost, MDL-646, CL-115,574, CL-115,347, TR-4161, TR-4752, TR-4367, CP-27987, sulprostone, gemeprost, alfaprostol, delprostenate, prostalene, fenprostalene, CL-116,069, ONO-995 and RO-229648, and their pharmaceutically acceptable esters and salts, as appropriate.

23) The method of claim 22 wherein the prostaglandin is selected from the group consisting of $PGF_{2\alpha}$-11-pivalyl ester, the 1-amido-15-methyl ether of $PGF_{2\alpha}$, 1-ethylamido-18,19,20-trinor-17-phenyl-$PGF_{2\alpha}$, $PGF_{2\alpha}$-1-ethyl ester, $PGF_{2\alpha}$1-isopropyl ester, the acid and isopropyl ester derivatives of $PGF_{2\alpha}$ wherein the omega chain has been replaced with phenylethylsulfonamidomethyl-, as represented by the structure below:



R=H, i-propyl, RO-229648, SQ 27986, ZK 138519, 13,14-dihydro-ZK 138519, ZK 110841, 13,14-dihydro-ZK 110841, PhXA41, and 18,19,20-trinor-17-phenyl-$PGF_{2\alpha}$-1-methyl ester.

24) The method of claim 21 wherein the alpha adrenergic agent is further selected from formula (I) to contain the groups of formula (II) wherein R2 is bromine or methyl and all other variables are defined as in claim 21.



formula (II)

25) The method of claim 23 wherein the alpha adrenergic agent is brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine).

26) The method of claim 24 wherein the alpha adrenergic agent is brimonidine (5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine).

27) The method of claim 21 wherein the prostaglandin is the 11-pivalyl ester of $PGF_{2\alpha}$ and the alpha adrenergic agent is brimonidine.